Section 112 Rejections

Definiteness Rejections

The previously-pending claims were rejected under Section 112 due to use of the words "including" and "containing." New claims 52-95 do not use the terms "including" or "containing".

Previously-pending claims were also rejected under Section 112 due to the use of the words "isomers, enantiomers, diastereomers, tautomers, pharmaceutically-acceptable salts, prodrugs, and solvates" thereof. The new claims employ such terms in the singular form only, thus addressing the 112 rejection to the extent it is based on the use of the plural form of these terms. Also, the new claims use the term "stereoisomer" is used in place of "isomers." One skilled in the field will understand the terms "stereoisomers, enantiomers, diastereomers, and tautomers" to refer to compounds having the same chemical formulae and molecular structures as the compounds defined in the claims, but possibly different arrangement(s) of atoms in space or in the case of tautomers, compounds in equilibrium. Definitions for these terms, their intended inclusion in the claims, and exemplary methods of preparation are set forth in the specification at page 34. The term "prodrug" is specifically defined at pp. 32-34. Not every species of compound covered by the claims needs to be capable of having a "prodrug" for applicant to claim prodrugs of claimed compounds. Exemplary salts are recited at page 7.

By claiming the stereoisomers, Applicant's intent is not to recite compositions but to recite chemical compounds reflected by the generic formulae and selections set forth in the claims, irrespective of their possible different arrangements in space.

Enablement Rejections

The Office Action rejects claims 19-30 on the ground that the specification, while enabling for rheumatoid arthritis, is not enabling for all p38 mediated diseases. It is suggested that evidence needs to be provided to support the claims to treating conditions associated with p38 activity. (OA at p. 4.)

The relative burdens of proof with regard to such rejections are set forth in MPEP § 2107.01, and in *In re Brana*, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Initially, the specification which discloses a manner of making and using the invention must be taken as in compliance with the enabling requirement unless the Examiner presents "reason to doubt the objective truth of the

statements contained therein...." The PTO "has the initial burden of challenging a presumptively correct assertion of utility in the disclosure." *In re Brana*, 34 USPQ2d at 1441; MPEP § 2107.01(b). Preferably this is done by citation of documentary evidence. MPEP 2107.01(c). Once the PTO presents such evidence, the burden shifts to the applicant to present rebuttal evidence, i.e. "suitable proofs" of utility. *In re Marzocchi*, 169 USPQ2d 367, 369 (CCPA 1971). The "suitable proofs" referenced in *Marzocchi* may include data obtained subsequent to filing the application. Although information cannot be added to the disclosure, data can be supplied post-filing "to demonstrate that the teaching in the specification is truly enabling." *In re Armbruster*, 512 F.2d 676, 185 USPQ 152, 155 (CCPA 1975).

Applicant contends that a *prima facie* case has not been established.

It is stated in the Office Action that "A very recent publication expressed that treating disease by the inhibition of p38 is still exploratory." (OA, p. 5).

However, no documentary evidence is provided to doubt the specification's presumptively correct assertion of utility. The Office Action suggests that the treatment of diseases such as Alzheimer's disease, multiple sclerosis, psoriasis, and other inflammatory conditions is "speculative" (OA, p. 4), and that use of p38 inhibitors to treat inflammatory conditions is "exploratory." (OA, p. 5). Under *In re Brana*, the "unpredictable" field of anti-tumor drugs did not satisfy the PTO's burden of challenging a presumptively correct assertion of utility. There, the Federal Circuit recently stated: "The purpose of treating cancer with chemical compounds *does not suggest an inherently unbelievable undertaking* or involve implausible scientific principles. . . . Modern science has previously identified numerous successful chemotherapeutic agents." 34 USPQ2d at 1439. *See also In re Cortright*, 49 USPQ2d 1464, 1466-67 (Fed. Cir. 1999) (the PTO cannot make a lack of enablement rejection unless the description suggests an inherently unbelievable undertaking or involves implausible scientific principles).

Use of p38 inhibitors to treat inflammatory conditions, including conditions such as Alzheimer's disease, multiple sclerosis, or psoriasis, is not an inherently unbelieveable undertaking or implausible scientific principle. In fact, there are presently a number of p38 inhibitors in Phase I and Phase II clinical trials and in development. (*See* enclosed.)

Accordingly, use of p38 inhibitors to treat inflammatory diseases is a well-accepted mechanism of action.

Additionally, even if a *prima facie* case were established, applicants submit they have rebutted it herein. The enablement requirement is satisfied where the specification teaches one skilled in the field how to make and use the invention without undue experimentation. *PPG Indus. Inc. v. Guardian Indus. Corp.*, 37 USPQ2d 1618, 1623 (Fed. Cir. 1996); *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). Enablement is a matter of degree which varies depending on the technology and the disclosure, *e.g.*, what would constitute "undue experimentation," given the circumstances. *PPG Indus.*, 37 USPQ2d at 1623.

The technology involved here is the use of compounds for inhibiting p38 kinase and treating diseases associated with p38 activity. While rheumatoid arthritis was initially identified (some years ago) as a disease that can be effectively treated with a p38 inhibitor, the state of the art today supports use of p38 inhibitors to treat many other diseases. In 1998, it was reported that "Ample evidence indicates that the p38 pathway serves an important role in inflammatory responses." *See* New *et al., "The p38 MAP Kinase Pathway and Its Biological Function,* TCM Vol. 8, No. 5, (1998) at p. 224. Two years ago, it was reported:

> The therapeutic utility initially proposed for p38 inhibitors was for treatment of inflammatory diseases, more specifically rheumatoid arthritis. . . . However, a broader involvement of p38 in disease is clear. For example, cellular data suggesting the potential involvement of p38 in disease has been reported for stroke, myocardial ischaemia, Alzheimer's disease, osteoarthritis, and lung injury. In animal models of disease, p38 inhibitors have demonstrated activity in models of septic shock, angiogenesis, and dermatitis.

Boehm *et al., "New Inhibitors of p38 Kinase,"* Expert Op. Ther. Patents, Vol. 10(1), 2000, at p. 34.

More recently, it was reported that p38 inhibitors have demonstrated effectiveness in animal models of endotoxin shock and bone resorption. (*See* Dumas *et al., "Synthesis and Pharmocological Characterization of a Potent, Orally Active p38 Kinase Inhibitor,"* Bioorganic & Medicinal Chemistry Letters, Vol. 12 (2002), at pp. 1559-1562). Various literature references provide data supporting the conclusion that p38 is linked to angiogenesis through cellular VEGF production and plays a significant role in adhesion molecule up-regulation, myocardial injury, and gastric disease. (*See* Dumas, *supra*; Gao *et al., "p38 MAPK Inhibition Reduces Myocardial Reperfusion Injury via Inhibition of Endothelial Adhesion Moelcule Expression and Blockade of*

PMN Accumulation," Cardiovascular Research, Vol. 53 (2002) at 414-422, and Slomiany *et al., Disruption in Gastric Mucin Sythesis, etc.,"* Biochemical and Biophysical Research Communications, Vol. 294 (2002) at pp. 220-24.) Further literature references are available reporting that p38 kinase is implicated in various other diseases and conditions.

Here, the specification provides competent evidence that the compounds were tested for their p38 activity and found to be effective inhibitors (at pp. 38-40). Assays for p38 inhibitoin and TNF-α production are described, and the activity of the compounds reported (p. 38). The specification lists a number of specific p38 conditions that the compounds are effective in treating which are supported by the literature (at pp. 35-37). Formulations and methods of administration are set forth (at p. 6-7). The specification provides sufficient guidance on how-to-make and how-to-use the invention, *i.e.*, the method of making, method of administration, and dosage units (p. 38) are stated.

Enablement is viewed with a rule of reason. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970). It would be unreasonable to require that applicants test each one of the compounds for every conceivable p38 disease against which the compounds would be effective and then specifically include in the claims reference to only those diseases and no others. For example, in *In re Bundy*, 209 USPQ 48 (CCPA 1981), the court reversed the PTO's rejection of the claims on enablement. There, a broad range of pharmaceutical uses was asserted; however, the specification did not provide specific support for each of the various biological purposes. *Id.* at 51 The court found the enablement rejection was in error, stating:

> Early filing of an application with its disclosure of novel compounds which possess significant therapeutic use is to be encouraged. Requiring specific testing of the thousands of prostaglandin analogs encompassed by the present claim in order to satisfy the how-to-use requirement of § 112 would delay disclosure and frustrate, rather than further, the interests of the public. *Id.* at 52.

By the same token, applicant here is not required to provide data regarding each one of the p38 mediated diseases referenced in the specification. The compounds were tested and shown to be effective in inhibiting p38 kinase and TNF-α. The specification provides sufficient guidelines on using the invention. *See Id.* at 51 ("sufficient guidelines as to use are given in the disclosure here").

Accordingly, it is respectfully requested that the enablement rejection be withdrawn.

Section 102 Rejections

Claims 1, 14, and 31 were rejected under Section 102(b) an anticipated by Schmitz (US Pat. No. 3,290,305), and claims 1, 2, 14, and 31 were rejection under Section 102(b) in view of Winter (US Pat. No. 3,867,383), Hoppe (US Pat. No. 4,617,390), Newton (US Pat. No., 5,062,882), and Raspanti (US Pat. Nos. 5,346,691 and 5,759,525).

Applicant submits that the new claims 52-95 distinguish over the cited references under Section 102.

Initially, applicant gratefully acknowledges that the Examiner gave individual treatment to the claims, considering the applicability of each cited reference to each claim. The treatment given the claims in the Office Action appropriately recognizes that dependent claims (or other claims following claim 1) are of different scope, and need to be analyzed for patentability separate from, claim 1 (now claim 52).

Notably, the Section 102(b) rejection was not applied to previously-pending claim 42, or to any of claims 32-42, each of which show R^9 as being attached to the phenyl ring (of R^6) in the meta position. Not one of Winter, Hoppe, or Raspanti allow for the possibility of a meta substitution at a corresponding location. New claim 52, and each claim following claim 52, shows R^9 in the meta position. Thus, Winter, Hoppe and the Raspanti are no longer applicable.

Schmitz in its generic formula refers to group X (corresponding to the phenyl ring R^6) as an aliphatic aminoacid group. Schmitz shows a number of examples for X which do not include a meta substituted phenyl. Schmitz's description of an aliphatic aminoacid group for X is too broad to constitute an anticipation of the meta substituted phenyl recited in the instant claims. *See Schering Corp. v. Precision-Cosmet Co.*, 614 F. Supp. 1368, 227 USPQ 278 (D. Del. 1985) ("The general rule is that a prior genus does not anticipate a later species") (citing I Chisum, *Patents* § 3.02[2] (1985), and *In re Ruschig*, 343 F.2d 965, 145 USPQ 274 (CCPA 1965)). *See also Ex Parte Westphal*, 223 USPQ 630, 632-33 (Bd. Pat. App. & Int'f. 1983) (genus defining 3-methylthio-4-amino-6-$C_{1\text{-}8}$*alkyl*-1,2,4-triazine-5-ones did not anticipate claim to 3-methylthio-4-amino-6-*tert-butyl*-1,2,4-triazine-5-one because the prior art "patent define[d] R_1, among other options, as *alkyl of 1 through 8 carbon atoms*, but d[id] not specifically name the *tert-butyl* radical").

Newton discloses a genus that could encompass a meta-substituted phenyl (*e.g.*, group Y, shown with no particular point of attachment). However, this *genus* does not provide a basis for an anticipation argument, for the reasons given above regarding Schmitz. Newton has a mandatory ortho-substituent (Z) on the phenyl ring, typically a group COR^3, wherein R^3 is alkoxy (alkoxycarbonyl group). In the Examples, Newton shows meta substituents of Me (Ex. 16), hydroxy (Ex. 32), triazinyloxy (Ex. 33), methoxy (Ex. 49), benzo-fused ring (Ex. 50), $N(Et)_2$ (Ex. 55), and chloro (Ex. 60). In each of these examples, the mandatory ortho-substituent (Z) is CO_2Me or CHO. In the instant claims, neither R^7 nor R^8 allows for selection of CHO or alkoxycarbonyl. Accordingly, Newton does not disclose a species falling in the claimed genus and does not anticipate.

Each of the claims 53-95 either depend from, or are more narrow than, claim 52. Thus, these claims are not anticipated by the cited references for at least the reasons referenced above.

Section 103 Rejection

Claims 1-7, 14 and 31-41 were rejected under Section 103(a) in view of Daeyaert *et al.*, US Pat. No. 6,150,360.

Applicant gratefully acknowledges that the subject matter of claims 12, 27, 28, 29 and 30 were found allowable over the art of record, having been rejected under Section 112 but not Sections 102-103. New claim 66 is similar in scope to claim 12 and thus, should be found to contain allowable subject matter (the 112 rejections having been addressed above).

Daeyaert discloses a triazine having the substituent $X\text{-}R^5$ or $X\text{-}Alk\text{-}R^6$ wherein the groups R^5 or R^6 may be phenyl, which may be substituted (or may be indanyl or indolyl.) The substituents on the R^5 or R^6 phenyl ring may be selected from a broadly-recited group that includes, generally, formyl, alkoxy, alkylcarbonyl, hyrdoxy, and alkoxycarbonyl. Also, there is attached to the triazine a second phenyl group having an optional substituent R_4, which may be selected from a group that includes hydroxy, halo, alkyl, alkoxy, cyano, aminocarbonyl, nitro, amino, trihalomethyl, or trihalomethoxy (col. 1, l. 65-67).

Accordingly, Daeyaert requires a biaryl (or aryl-heteroaryl) substituted triazine, wherein a phenyl group is bonded to the triazine via a nitrogen atom, and an aryl, indanyl, or indolyl is linked

to the triazine via a heteroatom, i.e., N, O, S, or S(=O) (the X groups) (this heteroatom can also be attached to an alkenylene linker of up to 4 carbon atoms.) In claims 55, 62, 63, 64, 65, 70 and 77, the selections for R^2, R^3 and R^{14} do not provide for a biaryl-sustituted triazine. Thus, these claims define compounds that are outside the scope of the broadest, generic formulae of Daeyaert. There is no suggestion in Daeyert of replacing one of the aryl/heteroaryl groups with a non-aromatic ring or non-ring group. Accordingly, it is submitted that Section 103 may not be applied to new claims 55, 62, 63, 64, 65, 70 and 77 based on Daeyert. Compare, *e.g.*, *Ex parte Ligett*, 121 USPQ 324, 326 (Bd. Pat. App. 1958) (holding an alkyl ester of N-phenyl maleamic acid unoobvious over an alkyl ester of N-napthyl maleamic acid because nothing in the art suggested the phenyl derivative would be expected to be as effective as the naphtyl derivative – both compounds used for fungicides).

With regard to claim 52, the genus defined by Daeyaert would cover an untold number of compounds, particularly given that the substituents R^4 and groups attached to R^5 and R^6 are generically identified as possibly including "alkoxycarbonyl" and "aminocarbonyl," with no examples or definitions given for these terms. Given the size of the genus in Daeyaert, it is appropriate to consider subgenuses and species in assessing obviousness. (*See* MPEP § 2144.08 (II).) A large genus does not render obvious all species of compounds that fall within the genus but only those species that are shown or fairly suggested when one considers preferred selections and species. *See In re Baird*, 16 F.3d 380, 29 USPQ2d 1550 (Fed. Cir. 1994), and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

Preferred subgenuses in Daeyaert each recite a *para*-substituted aminophenyl or aminopyridyl group attached to the triazine. The *para* substituent is cyano, aminocarbonyl, nitro, or trifluoromethyl (e.g., col. 2, lines 40-50), more preferably cyano, and there are no other substitutions on this phenyl or pyridyl ring. The R^5 or R^6 substituent is recited as being preferably selected from halo, lower alkyl, lower alkoxy, cyano, loweralkylcarbonyl, nitro, and trifluoromethyl (col. 4, l. 30-35). There is no suggestion that a meta substituent is preferred, nor is there a suggestion that it would be preferred to have a meta substituent of carboxy, carboxamide, or the like.

Applicant submits that the disclosed species in Daeyaert closest to the instantly-claimed compounds are Examples 10, 12, and 17, in Table 1, showing *para*-cyano substituents and meta substituents of methyl, bromo, and chloro, respectively; and Examples 2, 13, 15, 42, 48, 50, 53, 61,

66, 67, 80, 81, and 82, each of which shows the *para*-cyano substituent and a meta substituent selected from methyl, fluoro, bromo, chloro, methoxy, or amino.

No other meta substituents are shown or suggested in Daeyaert. The subgenuses and species of Daeyaert do not teach or suggest a mandatory meta substituent of a carboxamide, carboxy, or other such group. Although Daeyaert in few examples shows a meta substituent of methyl or amino, in that and all other examples in Daeyert, there is a *para*-cyano phenyl group. The present claims exclude such compounds.[1]

It is not obvious based on Daeyaert that selection of a different compounds wherein the phenyl group has a meta substituent of carboxy, carboxamide etc (R^9 groups) would have p38-inhibitory activity, considering, among other things, that in the field of pharmaceutically-chemistry, it is known that small changes in structure can have dramatic effects on pharmacological activity. *See, e.g., See Ex Parte Brouard*, 201 USPQ 538, 539 (Bd. Pat. App. & Int.'f 1976) ("we do not agree with the examiner that substitution of a hydrogen atom for a hydroxy group is *prima facie* obvious"); and *In re Wagner*, 371 F.2d 877, 881, 152 USPQ 552, 557 (C.C.P.A. 1967) (reversing Board's ruling that "the modification of a compound by the addition of one or more methyl groups is well known and thus obvious" because the Board failed to take into account biological or pharmaceutical properties of the compounds).

The remaining claims are not obvious in view of Daeyaert for at least the reasons stated above with respect to claim 52. Notably, in claims 53 and 54, there is no selection of a para-cyano substituted aminophenyl group attached to the triazine ring, unlike the preferred subgenus and species identified throughout Daeyaert. In claims 57, 58, 59, 61, 63, 65, and 67 through 77, there are particular selections recited for R^9 which are not taught or suggested in the cited references as a preferred or even possible *meta* substituent (as per claim 52).

[1] The proviso in claim 52 that R^2 and R^{14} may not be *para*-cyano phenyl when R^9 is methyl or amino is not new matter. *See In re Johnson*, 194 U.S.P.Q. 187 (C.C.P.A., 1977), where the C.C.P.A. reversed the rejection of claims under 35 U.S.C. §112, first paragraph, when the applicant had added provisos to his claims to exclude two prior art species. The C.C.P.A. reasoned that applicants frequently discover during the course of prosecution that only a part of what they invented and originally claimed is patentable and that, by adding provisos to his claims, Johnson merely excised the invention of another and did not claim "new matter." 194 U.S.P.Q. at 196.

Accordingly, applicant respectfully requests that the new claims 52-95 are not obvious in view of Daeyaert.

Double-patenting Rejection

Applicant is abandoning the parent case, 09/747,195, in favor of this CIP, thus rendering moot the double-patenting rejection.

Amendments to the Specification

The specification was amended to correct obvious typographical and formatting errors.

FEES

No fees should be due. Although 43 new claims are added, including three independent claims, two independent claims and a total of 51 claims have been canceled.

SUMMARY

In view of the foregoing, it is requested that this case proceed to issuance. The Examiner is invited to contact the undersigned if it is believed prosecution could be expedited. Attached hereto is a "Version with Markings to Show Changes Made" (i.e., showing the corrections to the specification).

Respectfully submitted,

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Date: September 16, 2002

Marked Up Version to Show Changes Made

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N-HETEROCYCLIC INHIBITORS OF TNF-ALPHA EXPRESSION

Cross Reference to Related Application

This application is a continuation-in-part of United States Patent Application Number 09/747,195, which claims priority to United States Provisional Patent Application Serial Number 60/173,227, filed December 28, 1999.

Field of the Invention

This invention relates to N-heterocyclic compounds that are effective in blocking cytokine production, and in particular the expression of TNF-alpha (TNF-α), via inhibition of p38 kinase. Compounds of the present invention are useful in the treatment of inflammatory diseases such as, for example, rheumatoid arthritis.

Background of the Invention

Overproduction of cytokines such as IL-1 and TNF-α is implicated in a wide variety of inflammatory diseases, including rheumatoid arthritis (RA), psoriasis, multiple sclerosis, inflammatory bowel disease, endotoxin shock, osteoporosis, Alzheimer's disease and congestive heart failure, among others [See Henry *et al.*, *Drugs Fut.*, 24:1345-1354 (1999); and Salituro *et al.*, *Curr. Med. Chem.*, 6:807-823 (1999)]. There is convincing evidence in human patients that protein antagonists of cytokines, such as, for example, monoclonal antibody to TNF-α (Enbrel) [Rankin *et al.*, *Br. J. Rheumatol.*, 34:334-342 (1995)], soluble TNF-α receptor-Fc fusion protein (Etanercept) [Moreland *et al.*, *Ann. Intern. Med.*, 130:478-486 (1999)] and/or IL-1 receptor antagonist [Bresnihan *et al.*, *Arthritis Rheum.*, 41:2196-2204 (1998)], can provide effective treatment for chronic inflammatory diseases. As none of the current treatments for inflammatory diseases provide complete relief of symptoms, and as most current treatments are associated with various drawbacks such as side effects, improved methods for treating inflammatory diseases are desirable.

TNF-α is a protein whose synthesis occurs in many cell types in response to an external stimulus, such as, for example, a mitogen, an infectious organism, or trauma. Signaling from the cell surface to the nucleus proceeds via several intracellular mediators including kinases that catalyze phosphorylation of proteins downstream in the signaling

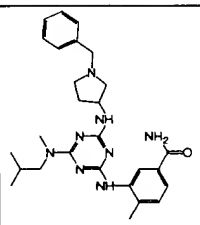
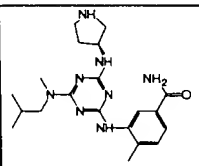
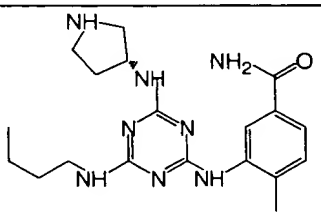
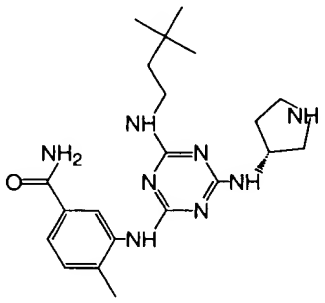
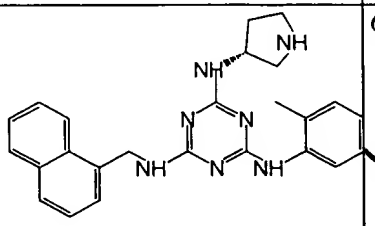
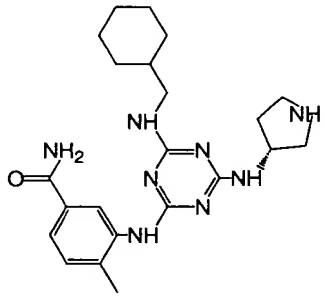
55	488.64		56	398.515	
57	384.488		58	412.542	
59	468.565		60	424.553	

Table 1

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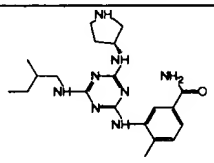
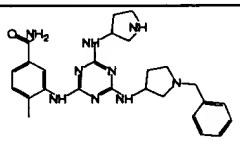
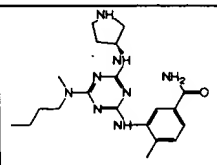
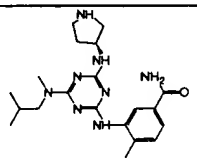
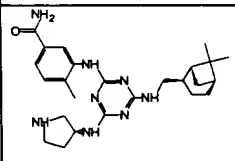
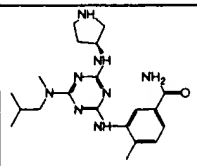
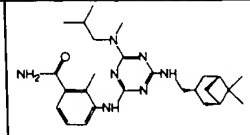
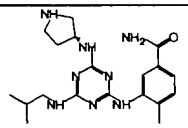
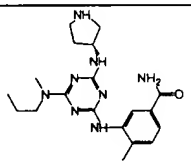
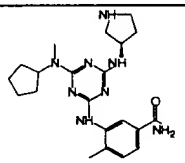
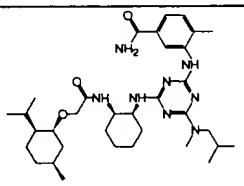
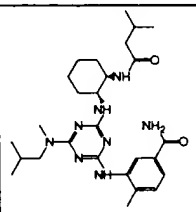
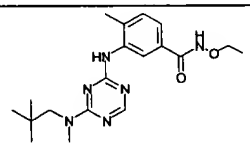
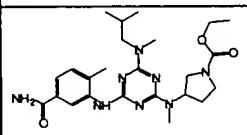
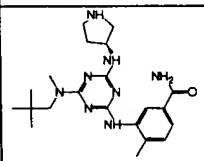
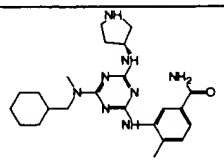
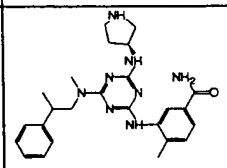
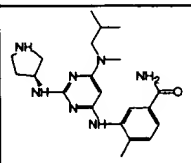
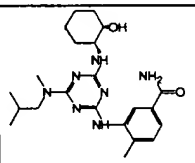
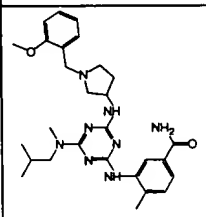
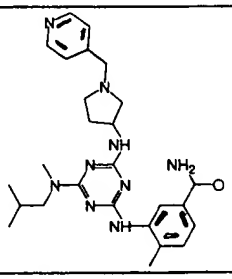
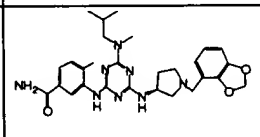
61	398.515		62	487.612	
63	398.515		64	398.515	
65	464.618		66	398.515	

67	465.646		68	384.488	
69	384.488		70	410.526	
71	622.859		72	510.687	
73	426		74	484.605	
75	412.542		76	438.58	
77	460.586		78	397.527	
79	427.553		80	518.666	
81	489.628		82	532.649	

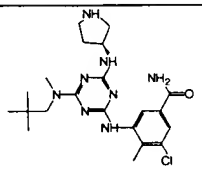
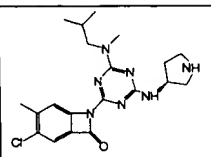
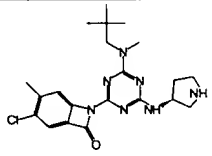
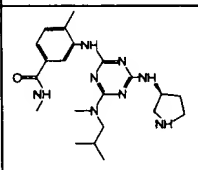
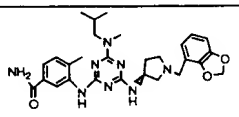
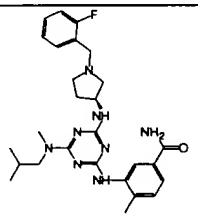
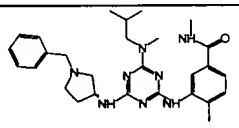
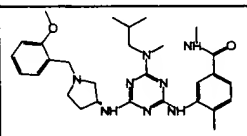
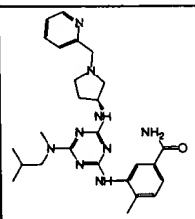
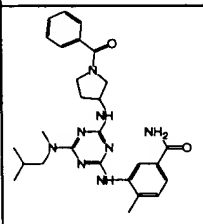
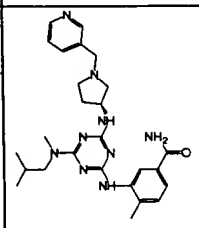
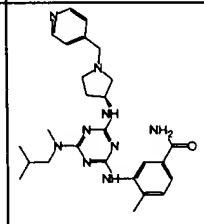
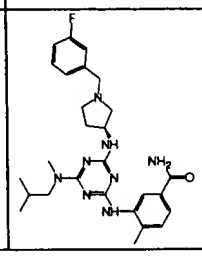
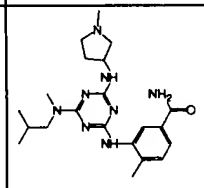
111	446.987		112	415.929	
113	429.956		114	412.542	

Table 1

#	MW		#	MW	
115	532.649		116	506.63	
117	502.667		118	532.693	
119	489.628		120	502.623	
121	489.628		122	489.628	
123	506.638		124	412.542	

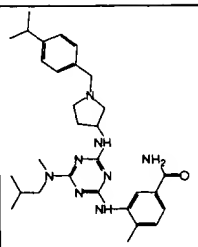
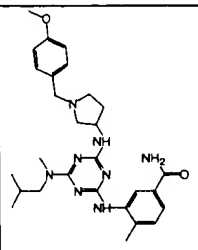
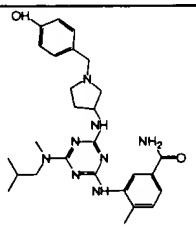
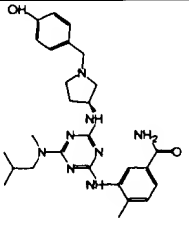
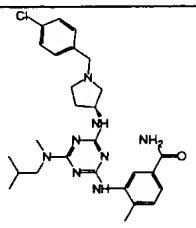
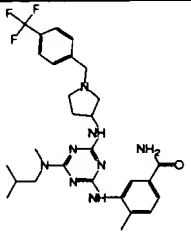
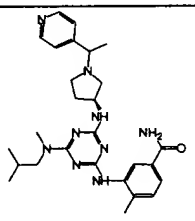
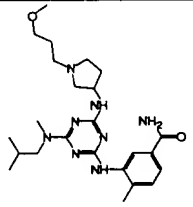
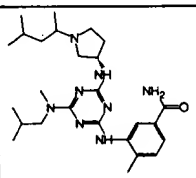
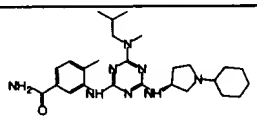
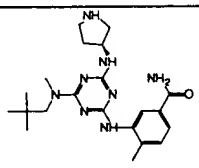
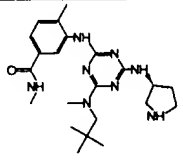
151	530.721		152	518.666	
153	504.639		154	504.639	
155	523.085		156	556.637	
157	503.655		158	470.622	

Table 1

#	MW		#	MW	
159	482.677		160	480.661	
161	412.542		162	426.569	

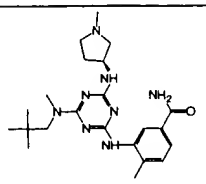
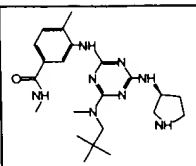
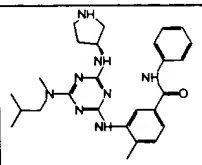
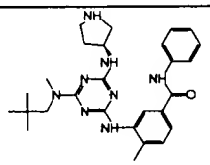
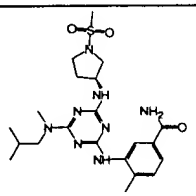
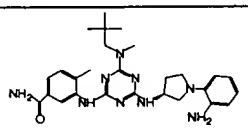
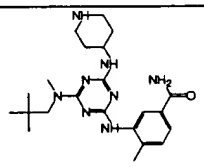
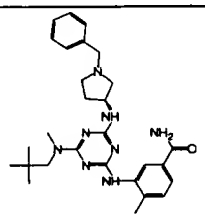
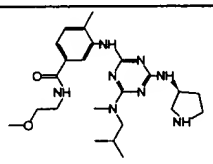
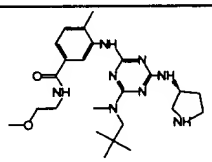
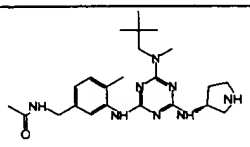
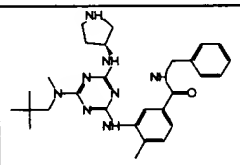
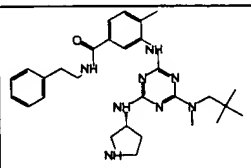
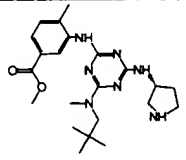
209	426.569		210	426.569	
211	426.569		212	488.64	
213	476.604		214	503.655	

Table 1

#	MW		#	MW	
215	426.569		216	502.667	
217	456.595		218	470.622	
219	440.596		210	502.667	
221	516.694		222	427.553	

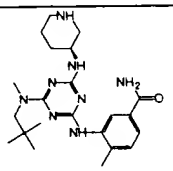
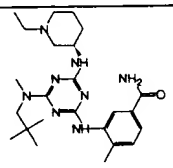
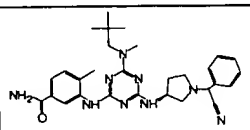
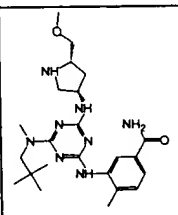
289	426.569		290	454.623	
291	527.677		292	456.595	

Table 1

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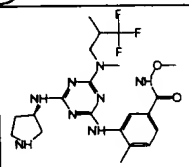
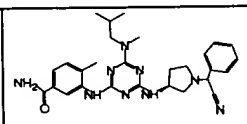
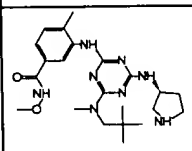
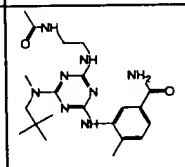
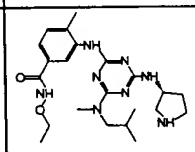
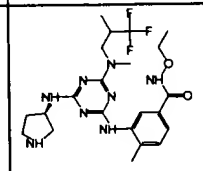
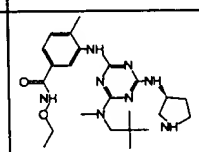
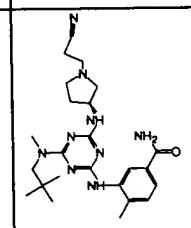
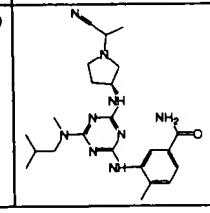
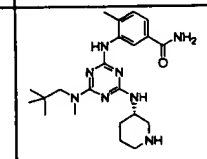
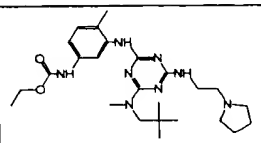
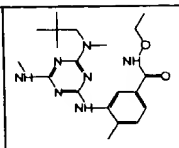
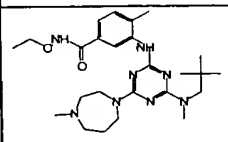
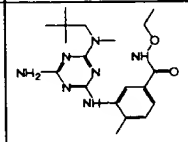
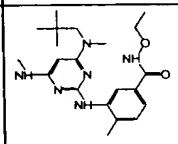
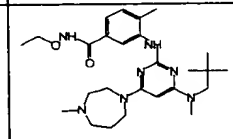
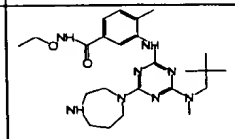
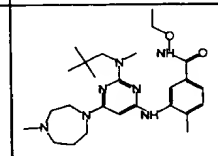
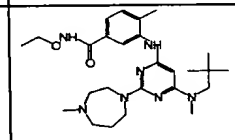
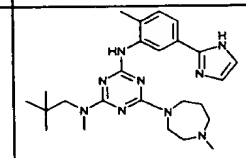
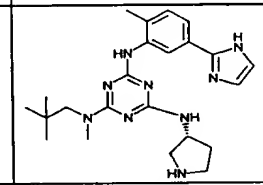
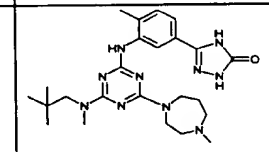
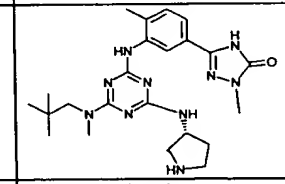
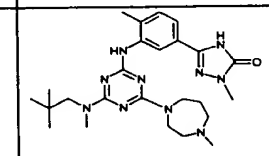
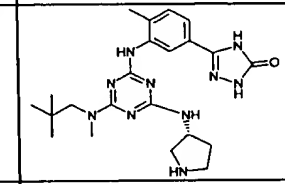
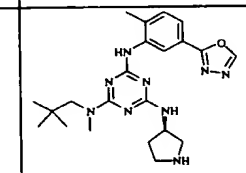
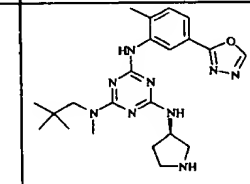
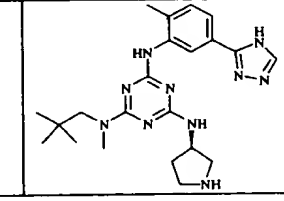
293	482.511		294	513.65	
295	442.568		296	428.541	
297	472.562		298	496.538	
299	456.595		300	465.606	
301	451.579		302	426.569	

355	484.649		356	401.515	
357	484.649		358	387.488	
359	400.527		360	483.661	
361	470.622		362	483.661	
363	483.661		~~400~~ 364	463.62	
~~401~~ 365	435.57		~~402~~ 366	480.61	
~~403~~ 367	466.58		~~404~~ 368	494.64	
~~405~~ 369	452.56		~~406~~ 370	437.54	
~~407~~ 371	450.58		~~408~~ 372	436.56	

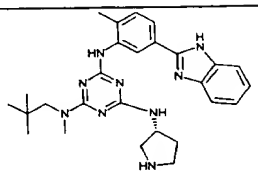
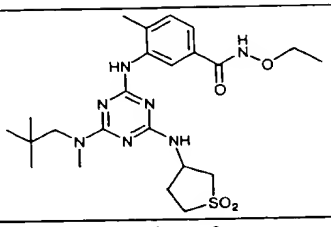
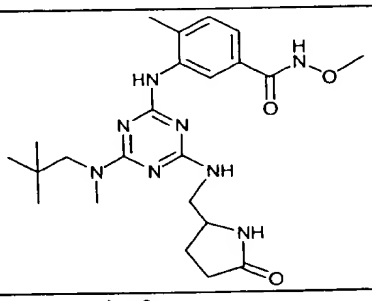
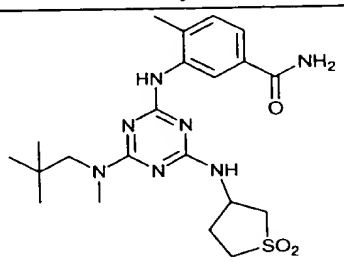
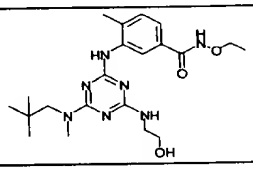
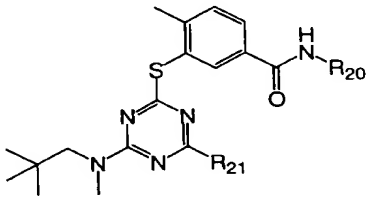
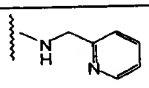
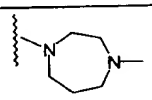
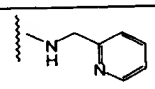
~~409~~ 373	485.63		~~410~~ 374	505.63	
~~411~~ 375	470.57		~~412~~ 376	491.61	
~~413~~ 377	440.59				

Table 2



#	R^{20}	R^{21}	Compound	HPLC Ret. Time(min)	Mass Spec MH^+(m/z)
~~364~~ 378	CH_3		O	2.89	466
~~365~~ 379	H		P	3.01	458
~~366~~ 380	H		Q	2.86	452

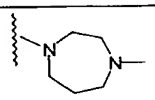
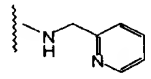
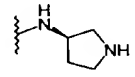
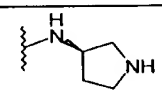
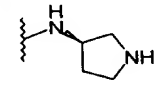
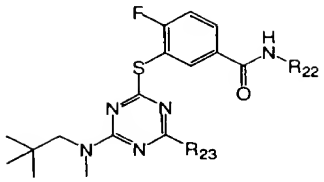
~~367~~ 381	OCH_3		R	2.99	488
~~368~~ 382	OCH_3		S	2.87	482
~~369~~ 383	OCH_3		T	2.80	460
~~370~~ 384	CH_3		U	2.80	444
~~371~~ 385	H		V	2.70	430

Table 3



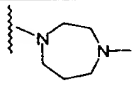
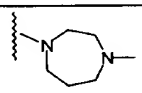
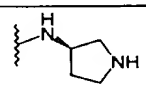
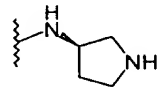
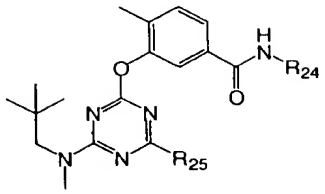
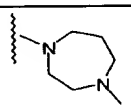
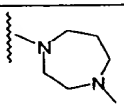
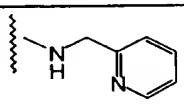
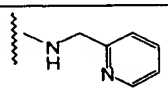
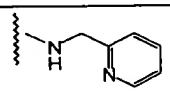
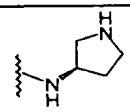
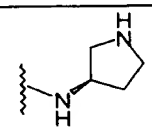
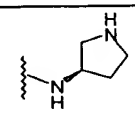
#	R^{22}	R^{23}	Compound	HPLC Ret. Time(min)	Mass Spec MH^+(m/z)
~~372~~ 386	H		C_1	2.27	445
~~373~~ 387	OCH_3		D_1	2.5	475
~~374~~ 388	H		E_1	1.99	417
~~375~~ 389	OCH_3		F_1	2.1	447

Table 4



#	R^{24}	R^{25}	Compound	HPLC Ret. Time(min)	Mass Spec MH^+ (m/z)
~~376~~ 390	CH_3		K_1	2.71	456
~~377~~ 391	OCH_3		L_1	2.68	472
~~378~~ 392	H		M_1	2.57	436
~~379~~ 393	CH_3		N_1	2.63	450
~~380~~ 394	OCH_3		O_1	2.61	466
~~381~~ 395	H		P_1	2.51	414
~~382~~ 396	CH_3		Q_1	2.59	428
~~383~~ 397	OCH_3		R_1	2.57	444